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FORMULATION AND EVALUATION OF OFLOXACIN FLOATING TABLETS BY USING HYDROXYL PROPYL METHYL CELLULOSE AS POLYMER

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ABSTRACT

Formulation of Gastro retentive dosage forms (GRDF) containing suitable drug candidates which would remain in the stomach and upper part or GIT for a prolonged period of time there by maximizing the drug release at desired site within the time before GRDFs left the stomach and upper part of the GIT, has provoked a great deal of increased interest in the formulation of such drug as (Floating drug delivery systems) FDDS. From the literature it is found that different grades of polymers such as Hydroxy propyl methyl cellulose (HPMC), Propyl methyl cellulose (PMC), Hydroxy ethyl cellulose (HEC), and Hydroxy propyl cellulose (HPC) were tried for design of controlled drug dosage forms by various matrix development techniques. Hence, in the present investigation it was aimed to test the suitability of using HPMC K_4M, $K_{15}M$ & $K_{100}M$ in the development of gastric retention system and for controlling the drug release from the matrix tablet. So by increasing the gastric retention of the dosage form in acidic medium may improve its bioavailability and hence it's therapeutic efficacy. The main objective of the present study is to design and evaluate the ofloxacin floating tablets. The present investigation describes the influence of content of hydroxyl propyl methyl cellulose Gastro retentive floating tablets by using different grade of hydroxyl propyl methyl cellulose. To evaluate the prepared tablets for physical parameters like weight variation, friability and hardness, Buoyancy test etc and to study the effect of floating properties of the buoyancy lag time (BLT) and total floating time (TFT) of ofloxacin floating matrix tablet. To evaluate the performance of the formulations using *in-vitro* dissolution study.To study the effect of tablet hardness on floating lag time. To ascertain the release mechanism and kinetics of drug release form tablet.

KEY WORDS: Ofloxacin, Hydroxy propyl methyl cellulose, Floating tablets.

1. INTRODUCTION

The goal of drug therapy is to produce drug concentration that elicit desired pharmacological action and minimize incidence and severity of unwanted adverse effects. To achieve this goal, it would be advantageous and more convenient to maintain a dosing frequency to once, or at most, a twice-daily regimen (Caldwell, 1998). In conventional oral drug delivery systems, there is little or no control over the release of the drug, and effective concentration of grossly excessive doses (Brahma, 2000). This kind of dosing pattern results in constantly changing, unpredictable, and often sub or supra therapeutic plasma concentrations, leading to marked side effects in some cases (Toshikiro and Kazutaka, 2002). Moreover, the rate and extent of absorption of drug from conventional formulations may vary greatly, depending on factors such as physiochemical properties of the drug, presence of excipients, various physiological factors such as the presence or absence of food, pH of the gastrointestinal (GI) tract, GI motility and so on. Uncontrolled rapid release of drug may cause local GI or systemic toxicity. Conventional dosage forms are rapidly absorbed, with the ascending and descending portions of the concentration versus time curve reflecting primarily the rate of absorption and elimination, respectively (Klausner,2003). Because of the rapid rate of absorption from conventional dosage forms, drugs are usually administered more than once daily, with the frequency being dependent on biological half-life ($t_{1/2}$) and duration of pharmacological effect (Patel,2007). The rate of dosing may also be affected by therapeutic index of a drug. To avoid many potential problems associated with the use of conventional dosage forms, controlled release concepts have been applied to the development of new dosage formulation a number of approaches have been used to increase the gastric retention time of a dosage form in stomach by employing a variety of concepts (Streubel, 2003). These includes: Floating Systems, Bio/Muco-adhesive systems, swelling and expanding system, Osmotic regulated systems (Ferdous Khan, 2008). There are 2 types of floating systems they are Effervescent floating system and Non - effervescent floating system. Ofloxacin inhibits an enzyme called DNA gyrase i.e. an essential component of the mechanism that passes genetic information onto daughter cells when a call divides. Is bactericidal and its

mode of action depends on blocking of bacterial DNA replication by binding itself to an enzyme called DNA gyrase, which allows the untwisting required to replicate one DNA double helix into two. Notably the drug has 100 times higher affinity for bacterial DNA gyrase than for mammalian (Shweta, 2008).

2. MATERIALS AND METHODS

2.1 Materials: Ofloxacin, Sodium bicarbonate and Di calcium phosphate was obtained as a gift sample from Micro Lab Ltd, Bangalore. Hydroxyl propyl methyl cellulose (k_4M, $K_{15}M$ & $K_{100}M$), Lactose, aerosol and hydrochloric acid were obtained as a gift sample from S.D. Fine chem. Ltd., Bombay. Talc and Magnesium stearate was obtained as a gift sample from Arvind Laboratories, Chennai. All other excipients and solvent used are of analytical grade.

2.2 Formulation of Ofloxacin floating tablets: Most powders cannot be compressed directly into tablets because the lack of proper characteristics of binding or together into a compact entity. Wet granulation is the process in which the liquid is added to powder equipped with any type of agitation that will produce granules. Main Steps Involved in the Wet granulation method, initially collect the material and passing through mesh #40 followed by milling of Drugs and Excipients. Mixing of Milled powders for a period of 30 minutes and prepare the binder solution by dissolving PVP k 90 in sufficient quantity of isopropyl alcohol. Mix the binder solution with powder mixer to form wet mass followed by drying of moist granules. Then Sieve the dried granules with lubricant and allow it to mix with Lubricant. Finally the prepared granules were compressed in 16 station Cadmach compression machine (Basak, 2004).

2.3 Evaluation of formulated Ofloxacin floating tablets: The prepared granules were evaluated for all the pre-formulation parameters and post compressional parameter. Compatibility studies have been done by FTIR. Swelling index of the floating tablet has been determined and the result has been tabulated in table number 6 (Narendra, 2006).

3. RESULTS

3.1 Compatibility studies by FTIR: Compatibility studies were performed using FTIR spectrophotometer. The FTIR spectrum of pure drug and physical mixture of drug and polymer were studied. The peaks obtained in the spectra's of each formulation correlated with the peaks of drug spectrum. From the FTIR spectrum, it was concluded that no significant shift in peak pattern in IR spectrum of drug, polymer, excipients.

3.2 Pre-formulation studies for the Raw materials: The values obtained for angle of repose for F1-F6 are tabulated in Table. The values were found to be in the rage 28˚.39′ to 38˚.36′. This indicates good flow property of the powder blend. As the concentration of HPMC K_4M, HPMC $K_{15}M$, HPMC $K_{100}M$ increases, the angle of repose and Carr's index increase while the flow rate decrease. Compressibility index was in the range between 13.93% to 39.24% indicating that the powder blends have good flow property was tabulated in Table 2.

3.3 Pre-formulation of prepared granules: The bulk density of the prepared granules was found to be in the range of 0.4 to 0.5 g/cm^2, were the tap density was found to be in the range of 0.5 to 0.6 gm/ml. The compressibility index was found to in the range of 16 to 21.69 and Hauser's ratio around 1.1 to 1.5. The angle of repose was found to be the range of 27˚12′ to 30˚25' was tabulated in table 3.

3.4 Post- compressional studies for granules: Floating tablet of Ofloxacin was prepared by direct compression method. Microscopic examination of tablets from each formulation batches has showed cylindrical shape (oval) with no cracks. The entire tablet passed weight variation test as the percentage weight variation was within the pharmacopoeial specification. The weights of all the tablets were found to be uniform with low standard deviation values as shown in Table. The measured hardness of tablet of each batch ranges 6 ± 1kg/cm^2 as shown in Table 4. The percentage amount of drug release was found to be within the I.P. limit of 90% to 110% of Ofloxacin.

3.5 Swelling Index: In the present study, the higher swelling index was found for tablets of FIIIB containing 30% HPMCK_{100}M. Thus, the concentration of polymer and ratio of lactose had major influence on swelling process, matrix integrity, as well as floating capability, hence from the above results it can be concluded that linear relationship exists between swelling process and concentration ratio as shown in Table & Figure. From the *in-vitro* drug profiles, it was found that drug release rate increased as the concentration of HPMCK_4 M increased. It was also concluded that the drug release rate was decreased by HPMC K_4M, HPMC $K_{15}M$, as that of lactose. The rate of drug release increased as tabulated in Table 5.

4. CONCLUSION

In the present investigation gastric retentive system of Ofloxacin were prepared with HPMC K_4M, HPMC $K_{15}M$ and HPMC $K_{100}M$ polymers. Ofloxacin has site-specific absorption in the upper part of the stomach and hence these systems are useful in the improving the absorption of the drug. An attempt was made to deliver Ofloxacin via floating drug delivery system could be formulated as an approach to increase gastric residence time and there by improve its bioavailability. For the formulation of floating drug delivery system polyethylene oxide was made as the hydrophilic matrix- forming polymer. The floating tablets were prepared using different polymer grade like that HPMC K_4M, HPMC $K_{15}M$ and HPMC $K_{100}M$ polymers. The grades of HPMC increased the viscosity by increasing the time of drug release (decrease the drug release). Tablet was subjected to various evaluation parameters such as physical property, floating property, swelling property, and in-vitro drug release studies. It was revealed that all batches had acceptable physical parameters. All tablet formulation had good floating property along with swelling behaviors and *in-vitro* drug release.

Table no 1 Formulation table of Ofloxacin floating tablets

Ingredients	F1	F2	F3	F4	F5	F6
Ofloxacin	400 mg	400 mg	400 mg	400 mg	400 mg	400 mg
HPMC K_4M	175mg	175mg	-	-	-	-
HPMC $K_{15}M$	-	-	175mg	175mg	-	-
HPMC $K_{100}M$	-	-	-	-	175mg	175mg
Lactose	44.5mg	44.5mg	44.5mg	44.5mg	44.5mg	44.5mg
Sodium Bi-Carbonate	70 mg	70 mg	70 mg	70 mg	70 mg	70 mg
PVP K_{90}	3.5 mg	3.5 mg	3.5 mg	3.5 mg	3.5 mg	3.5 mg
Isopropyl alcohol	0.1 ml	0.1 ml	0.1 ml	0.1 ml	0.1 ml	0.1 ml
Talc	2mg	2mg	2mg	2mg	2mg	2mg
Aerosol	2 mg	2 mg	2 mg	2 mg	2 mg	2 mg
Magnesium stearate	5 mg	5 mg	5 mg	5 mg	5 mg	5 mg

Table no 2 Pre-formulation studies for the Raw materials

Contents	Bulk density (gm/ml)	Tap density (gm/ml)	Compressibility index	Hausner's ratio	Angle of repose (θ)
Ofloxacin	0.425	0.623	17.89	1.21	29˚.45′
$HPMCK_4M$	0.365	0.527	34.20	1.49	30˚.35′
$HPMCK_{15}M$	0.523	0.685	18.56	1.45	38˚.36′
$HPMCK_{100}M$	0.895	1.316	36.70	1.23	54˚.12′
Lactose	0.436	0.458	39.24	1.68	29˚.86′
Sodium-bi-carbonate	0.895	1.316	36.70	1.58	30˚.85′
$PVPK_{90}$	0.359	0.456	13.93	1.47	28˚.39′
Talc	0.456	0.651	31.92	1.27	30˚.96′
Aerosil	0.785	0.426	20.58	1.63	28˚.86
Magnesium stearate	0.436	0.527	14.20	1.45	29˚.86′

Table no 3 Pre-formulation of prepared granules

Batch code	Bulk density (g/ml)	Tap density (g/ml)	Compressibility index (%)	Hausner's ratio	Angle of repose (θ)
F1	0.458	0.589	16.33	1.23	27˚.65′
F2	0.469	0.698	17.12	1.49	28˚.63′
F3	0.502	0.756	18.96	1.23	27˚.12′
F4	0.456	0.603	18.02	1.16	29˚.64′
F5	0.523	0.631	21.69	1.58	29˚.89′
F6	0.536	0.689	20.36	1.25	30˚.25′

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Table no 4 Physical properties of Ofloxacin matrix floating tablets

code	Evaluation parameters			
	Average wt. (mg)	Hardness (Kg/cm^2)	Percentage Friability(%)	Drugcontent(% w/w)
F1	700±1.52	5.5	0.532	98.42
F2	700±1.80	5.0	0.658	99.50
F3	700±1.63	6.5	0.498	101.20
F4	700±1.23	6.0	0.456	98.27
F5	700±1.05	7.5	0.374	98.50
F6	700±1.65	7.0	0.412	97.98

Table no 5 Floating properties of Ofloxacin matrix floating tablet Formulations

Batch code	Floating lag time (sec)	Total floating time (hr)
F1	5.0	12<
F2	4.5	10<
F3	5.5	12<
F4	5.0	12<
F5	5.5	12<
F6	6.0	12<

Table no 6 Swelling index of Ofloxacin tablet Formulations

Time (min)	Amount of drug dissolved					
	F1	F2	F3	F4	F5	F6
1	78	90	86	95	90	102
2	82	98	103	116	121	138
3	90	119	116	129	144	152
4	112	125	131	156	165	176
5	129	141	156	178	185	192
6	138	156	181	215	221	236
7	156	172	198	248	256	265
8	172	191	232	268	272	294

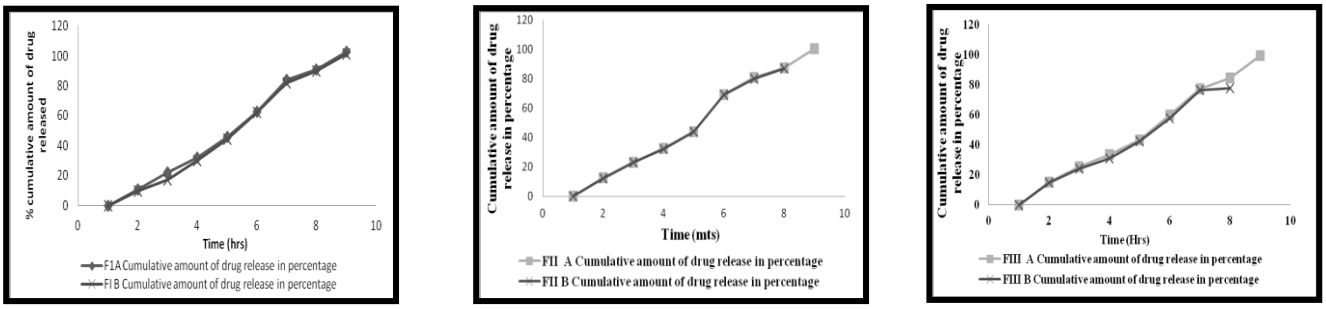

Figure no 1 *In-vitro* dissolution profile of the Ofloxacin floating tablet of F1, F2, F3, F4, F5 and F6

Table no 7 *In-vitro* dissolution profile of the Ofloxacin floating tablet of F1 and F6

Formulation		30 min	1 hr	2 hr	4 hr	6 hr	10 hr	12 hr	24 hr
F1	Cumulative amount of drug release (mg/ml)	42.76	88.6	128.32	183.28	249.48	335	362.52	411.4
	Cumulative amount of drug release in %	10.69	22.15	32.08	45.82	62.37	83.75	90.63	102.85
F2	Cumulative amount of drug release (mg/ml)	37.68	69.24	120.16	177.2	247.44	327.88	359.44	405.28
	Cumulative amount of drug release in %	9.42	17.31	30.04	44.30	61.86	81.97	89.86	101.32
F3	Cumulative amount of drug release (mg/ml)	50.08	92.08	130.72	175.84	276.6	323.24	348.8	400.8
	Cumulative amount of drug release in %	12.52	23.02	32.68	43.96	69.15	80.81	87.2	100.2
F4	Cumulative amount of drug release (mg/ml)	48.04	91.64	128.72	174.76	275.6	320	348	399.92
	Cumulative amount of drug release in %	12.01	22.91	32.18	43.69	68.95	80	87	99.98
F5	Cumulative amount of drug release (mg/ml)	61.16	100.8	134.4	173.12	239.28	306.56	338.08	397.12
	Cumulative amount of drug release in %	15.29	25.20	33.60	43.28	59.82	77.14	84.53	99.28
F6	Cumulative amount of drug release (mg/ml)	59.08	95.72	124.24	170.04	230.12	304.48	310.56	389
	Cumulative amount of drug release in %	14.77	23.93	31.06	42.51	57.5	76.12	77.64	81.25

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